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(54) Title: PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE

(57) Abstract

A process for the preparation of methyl 3–chloro–3H–indole–3–carboxylate, which comprises reacting an appropriate 3–carboxylate indole compound with N–chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11.

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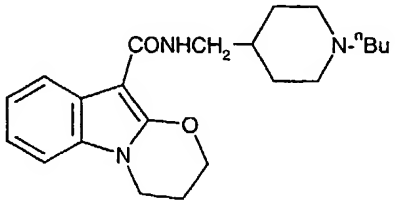
PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE

This invention relates to a new synthetic process to a compound having pharmacological activity.

WO 93/18036 (SmithKline Beecham plc) describes certain indole compounds having 5-HT_4 receptor antagonist activity including the compound of formula (I)

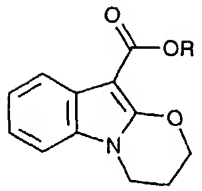


(I)

and its pharmaceutically acceptable salts. This compound is N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, referred to herein by its code number SB-207266, (the hydrochloride salt is SB-207266-A), which is being developed by SmithKline Beecham plc as the active ingredient in a medicament for treatment of irritable bowel syndrome.

Example 3 of WO 93/18036 describes a method of preparation of SB-207266-A from N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide (i.e. the compound corresponding to SB-207266, without the oxazino moiety), by reacting with N-chlorosuccinimide and 3-bromo-1-propanol, followed by treatment with sodium carbonate. N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide is prepared by coupling N-(1-^{n}butyl-4-piperidyl)methylamine with a indole-3-carboxylic acid.

WO 98/07728 (SmithKline Beecham plc) describes a process for preparing SB-207266-A which involves the use of the N-(1-^{n}butyl-4-piperidyl)methylamine intermediate at a later stage in the process thus resulting in an increased yield of SB-207266-A relative to the amount of this intermediate, which is relatively expensive to produce. In particular, the alternative process comprises the reaction of of N-(1-^{n}butyl-4-piperidyl)methylamine with a compound of formula (A):

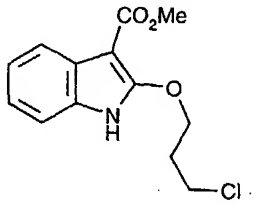


(A)

wherein R is alkyl, such as methyl or ethyl.

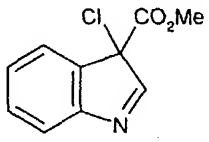
The compound of formula (A) wherein R is methyl is methyl 3,4-dihydro-2*H*-[1,3]-oxazino[3,2-*a*]indole-10-carboxylate.

WO98/07728 also describes the preparation of the oxazinoindole compound of the formula (A) from the corresponding indole by reaction with N-chlorosuccinimide and a 3-halo-propanol, such as 3-chloropropanol or 3-bromopropanol followed by cyclisation of the intermediate (B) by treatment with base in a suitable solvent.



(B)

The Description in the latter specification describes in more detail the preparation of compound (B) from the corresponding methyl indole-3-carboxylate by reaction of the latter with N-chlorosuccinimide in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to form an intermediate of formula (C):

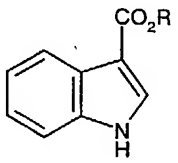


(C)

and subsequent reaction of (C) with 3-chloropropanol in the presence of methane sulphonic acid.

We have now found that the replacement of DABCO by a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11, especially 1,4-dimethylpiperazine, results in significant advantages for the commercial operation of the above reaction.

According to a feature of the present invention we provide a process for the preparation of the compound of formula (C) above, namely methyl 3-chloro-3H-indole-3-carboxylate, which comprises reacting a compound of formula (D) :



(D)

(in which R is as hereinbefore defined)

with N-chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11, especially 1,4-dimethylpiperazine (DMP).

Other examples of preferred bases for use in accordance with the invention are tetramethylethylenediamine and N-methylpiperidine.

The use of the above amine in place of DABCO has been found to increase significantly the overall yield of the process. The former amine also has the following advantages over DABCO:-

a) it is non-hygroscopic;

b) it does not react with dichloromethane, a preferred solvent for the reaction;

c) the product (C) is more stable allowing extended addition times and better temperature control;

d) quicker wash separations are possible during commercial manufacture; and

e) levels of the corresponding 2-methoxy compound, as an impurity, do not increase with extended process times.

The reaction is conveniently effected in an organic solvent such as dichloromethane or chloroform at a temperature in the range -20° C to +20° C.

The resulting product of formula (C) can be used for the next step in the synthesis of SB-207266 e.g as described in WO 98/07728 without any need for isolation or purification.

The following Example illustrates the invention.

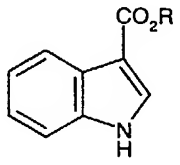
Example

Methyl 2-(3-chloropropoxy)-indole-3-carboxylate (formula (B))

A mixture of methyl indole-3-carboxylate and dichloromethane is cooled to 0° C. 1,4-dimethylpiperazine (0.55eq.) and N-chlorosuccinimide (1.1 eq) are added and the mixture left to stir for two hours to give slurry containing the compound of formula (C) above. The resulting slurry is added to a solution of 3-chloropropanol (1.1 eq) and trichloroacetic acid (0.12 eq) in dichloromethane, maintaining the temperature below 0° C. The reaction mixture is left to stir for half an hour, then washed with 10% aqueous sodium carbonate, 0.5 M hydrochloric acid and water. The organic solution is dried over sodium sulphate, filtered and the solvent evaporated. Toluene is added and the mixture stirred at 0-5° C for one hour. The product is then filtered, washed with toluene and dried to give the title product in 83 % yield.

Claims

1. A process for the preparation of methyl 3-chloro-3H-indole-3-carboxylate, which comprises reacting a compound of formula (D) :



(D)

(in which R is alkyl)

with N-chlorosuccinimide in the presence of a tertiary amine which is less nucleophilic than DABCO and which has a pK_b of from 8 to 11.

2. A process as claimed in claim 1 in which the amine is 1,4-dimethylpiperazine.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 99/04943

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 07728 A (SMITHKLINE BEECHAM PLC) 26 February 1998 (1998-02-26) cited in the application page 8, line 21 -page 10	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1999	08/11/1999

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INTERNATIONAL SEARCH REPORT

..formation on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9807728 A	26-02-1998	AU 4204897 A	06-03-1998
		CZ 9900516 A	14-07-1999
		EP 0922048 A	16-06-1999
		NO 990697 A	15-02-1999
		PL 331647 A	02-08-1999